Quinolizidines. XII. Synthetic Incorporation of Ethyl Cincholoiponate into a Tricyclic Intermediate Adaptable to Chiral Syntheses of the 10-Hydroxy-9-methoxybenzo [a] quinolizidine-Type Alangium Alkaloids

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Quinolizidines. XII.[1] Synthetic Incorporation of Ethyl Cincholoiponate into a Tricyclic Intermediate Adaptable to Chiral Syntheses of the 10-Hydroxy-9-methoxybenzo[*a*]quinolizidine-Type *Alangium* Alkaloids

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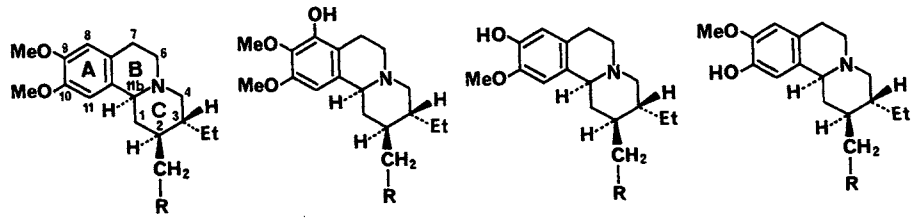
For the purpose of securing a key intermediate for chiral syntheses of the 10-hydroxy-9-methoxybenzo[*a*]quinolizidine-type *Alangium* alkaloids (type **4**), the tricyclic ester (−)-**15** has been synthesized from ethyl cincholoiponate [(+)-**6**] and 4-benzyloxy-3-methoxyphenacyl bromide by the "cincholoipon-incorporating method" through the intermediates (+)-**7**, **10**, **8**, (−)-**11**, (−)-**12**, (+)-**13**, (+)-**14**, (+)-**17**, and **16**.

Keywords——*Alangium* alkaloid synthesis intermediate; cincholoipon ethyl ester; mercuric acetate–edetic acid oxidation; regioselective lactam formation; thermal *cis–trans* isomerization; sodium borohydride reduction; catalytic hydrogenolysis; Fischer–Speier esterification; phenolic *O*-benzylation; Bischler–Napieralski cyclization

Alangium lamarckii THWAITES (family Alangiaceae) is a deciduous shrub or small tree widely distributed throughout India, Burma, Ceylon, South China, Malaya, and the Philippines.[2,3] Various parts of this plant have been used in the indigenous Indian systems of medicine for a long time.[2-4] The plant has so far been found to contain seventeen benzo[*a*]quinolizidine alkaloids and nine other alkaloids.[5] These benzo[*a*]quinolizidine-type *Alangium* alkaloids fall into four categories according to their substitution patterns in the aromatic ring A: (a) 9,10-dimethoxy type (**1**) (*e.g.*, emetine, cephaeline, tubulosine, protoemetinol, *etc.*); (b) 8-hydroxy-9,10-dimethoxy type (**2**) (*i.e.*, ankorine, alangicine, and alangimarckine); (c) 9-hydroxy-10-methoxy type (**3**) (*e.g.*, desmethylpsychotrine, 9-demethylprotoemetinol, *etc.*); (d) 10-hydroxy-9-methoxy type (**4**) (*e.g.*, demethyltubulosine, 10-demethylprotoemetinol, *etc.*).[5] We have already shown that the racemic synthesis of all of these types of alkaloids is possible by the "lactim ether method"[5-12] and the chiral synthesis,



1 **2** **3** **4**

R=CH_2OH or a heterocyclic ring

by the "cincholoipon-incorporating method".[1,5,9,12-16] In this paper, we present the details of a study on the synthetic incorporation of ethyl cincholoiponate [(+)-**6**] into the tricyclic

ester (−)-**15**, a key intermediate for syntheses of the **4**-type *Alangium* alkaloids. A preliminary account of this work has been reported.[17]

Condensation of (+)-**6**,[18] prepared from commercially available cinchonine (**5**)[19] in 50% overall yield according to the classical degradation procedure,[18a,20] with 4-benzyloxy-3-methoxyphenacyl bromide in hot benzene containing K_2CO_3 furnished the amino ketone (+)-**7** in 98% yield. Reduction of (+)-**7** with $NaBH_4$ in EtOH gave a diastereomeric mixture of the amino alcohol **10** in 97% yield. Oxidation of the mixture **10** with mercuric acetate–

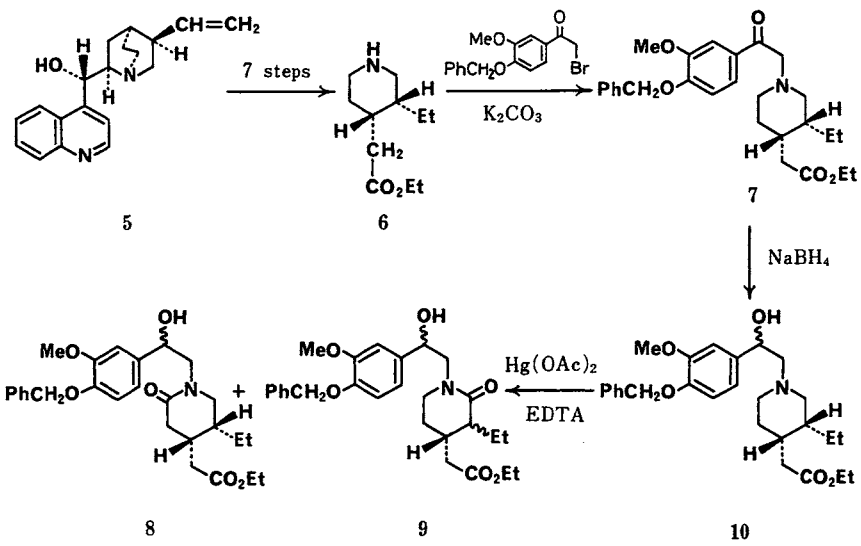


Chart 1

ethylenediaminetetraacetic acid (EDTA) in boiling 1% aqueous AcOH and column chromatographic separation of products afforded the 6-piperidone **8** as a diastereomeric mixture (53% yield) and an oily substance (15% yield) presumed[1,13,14] to be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones **9**. The two piperidone structures were assignable by analogy with the similar oxidation products of structurally analogous systems[1,13,14] and simpler 3-alkylpiperidine derivatives,[21] and the following self-consistent reaction sequence supported the correctness of these assignments.

Catalytic hydrogenolysis of the diastereomeric mixture of **8** with hydrogen activated on Pd–C catalyst in EtOH containing a little 70% perchloric acid produced the lactam phenol (−)-**11** in 99% yield. On hydrolysis with 2 N aqueous NaOH in EtOH at 25 °C, (−)-**11** gave the *cis*-lactam acid (−)-**12** in 98% yield. Thermal isomerization of (−)-**12** to the *trans*-lactam acid (+)-**13** was patterned after those reported previously[1,13,14,22] for structurally parallel systems. Thus, (−)-**12** was heated neat at 180 °C for 90 min to form an equilibrated mixture of the *cis* and the *trans* isomers,[22] from which the *trans*-lactam acid (+)-**13** was isolated by crystallization. The yield of (+)-**13** reached 74% when the *cis*-lactam acid recovered from the reaction mixture was repeatedly subjected to the same thermal reaction. On treatment with ethanolic HCl under the previously reported Fischer–Speier esterification conditions,[23] (+)-**13** gave the lactam ester (+)-**14** in 99% yield. The structure of (+)-**14** was confirmed by the spectral and thin-layer chromatographic (TLC) identity of this chiral compound with the known racemic *trans*-lactam ester (±)-**14**.[10]

Conversion of (+)-**14** into the benzyl ether (+)-**17** was effected in 96% yield by treatment of the former with benzyl bromide and K_2CO_3 in boiling acetone. Compound (+)-**17** was then cyclized with $POCl_3$ in boiling toluene, and the resulting iminium salt **16** was

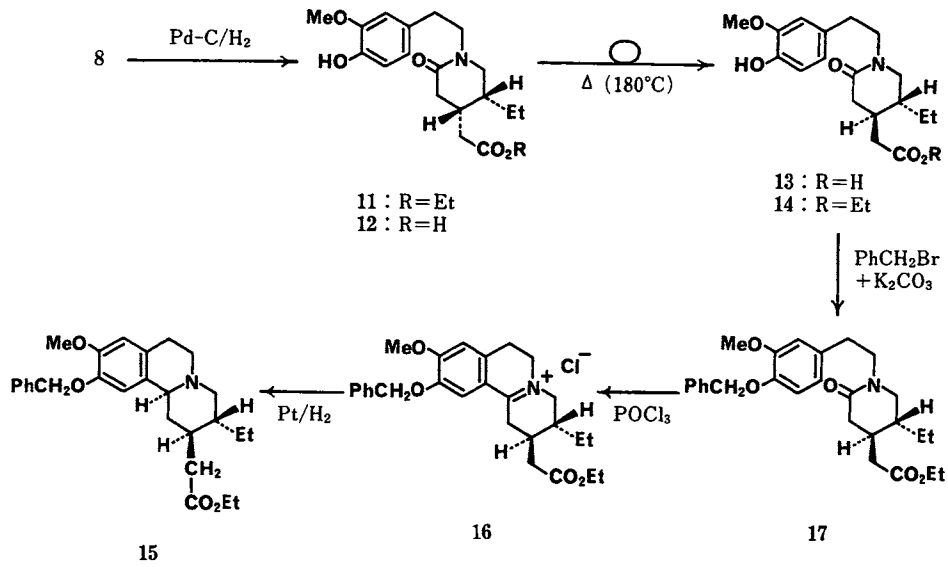


Chart 2

hydrogenated in EtOH with hydrogen and Adams catalyst to produce the desired tricyclic ester (−)-**15** in 70% overall yield from (+)-**17**. The TLC behavior and the solution infrared (IR) and nuclear magnetic resonance (NMR) spectra of (+)-**17** and (−)-**15** thus obtained were identical with those of the corresponding racemic varieties,[10] substantiating the assigned structures and stereochemistry.

In conclusion, the key intermediate (−)-**15** for chiral syntheses of the 10-hydroxy-9-methoxybenzo[*a*]quinolizidine-type *Alangium* alkaloids (type **4**) has now become available from ethyl cincholoiponate [(+)-**6**] in 24% overall yield through the above "cincholoipon-incorporating route." We have synthesized (−)-10-demethylcephaeline[16] and (−)-10-demethylprotoemetinol[12] from this intermediate, and the details will be reported elsewhere in the near future.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer at 24 °C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-SL polarimeter. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br=broad, d=doublet, dd=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, t=triplet.

(3*R*,4*S*)-(+)-1-(4-Benzyloxy-3-methoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(+)-7]——A mixture of ethyl cincholoiponate [(+)-**6**][18a,20] (4.98 g, 25 mmol), anhydrous K_2CO_3 (3.46 g, 25 mmol), 4-benzyloxy-3-methoxyphenacyl bromide[24] (8.38 g, 25 mmol), and benzene (100 ml) was stirred at 50—55 °C for 7 h. After cooling, the reaction mixture was washed successively with H_2O, 5% aqueous NaOH, and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to leave a reddish-brown oil (11.1 g, 98%). A portion of the oil was purified by column chromatography [alumina, hexane–AcOEt (3:1, v/v)] to give (+)-**7** as a pale yellow oil, $[\alpha]_D^{16}$ +3.7° (*c*=2.71, EtOH); mass spectra (MS) *m/e*: 453 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (ester CO), 1670 (ArCO); NMR ($CDCl_3$) δ: 0.84 (3H, t, *J*=7.1 Hz, $CH_2\underline{Me}$), 1.25 (3H, t, *J*=7.1 Hz, $OCH_2\underline{Me}$), 3.69 (2H, s, $ArCOC\underline{H}_2$), 3.93 (3H, s, OMe), 4.13 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2Me$), 5.22 (2H, s, $OC\underline{H}_2Ph$), 6.87 (1H, d, *J*=9.0 Hz, $H_{(5')}$), 7.25—7.5 (5H, m, Ph), 7.62 (1H, d, *J*=2.0 Hz, $H_{(2')}$), 7.64 (1H, dd, *J*=9.0 and 2.0 Hz, $H_{(6')}$).

(3*R*,4*S*)-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester (10)

——A solution of (+)-**7** (6.26 g, 13.8 mmol) in EtOH (60 ml) was stirred under ice-cooling, and $NaBH_4$ (522 mg, 13.8 mmol) was added portionwise over a period of 10 min. After stirring was continued at 0—5 °C for 2 h and then at room temperature for 6 h, acetone (3 ml) was added and the mixture was concentrated *in vacuo*. The residual yellow jelly was partitioned between H_2O and benzene. The benzene extracts were washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated to leave a diastereomeric mixture of **10** (6.07 g, 97%) as a faintly yellowish solid, mp 45—70 °C; $[\alpha]_D^{18}$ −1.6° (*c*=2.55, EtOH); MS *m/e*: 455 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (OH), 1726 (ester CO); NMR ($CDCl_3$) δ: 0.93 (3H, t, *J*=7.1 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, *J*=7.1 Hz, $OCH_2\underline{Me}$), 3.1 (1H, br, OH), 3.90 (3H, s, OMe), 4.14 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2Me$), 4.55—4.75 [1H, m, $ArC\underline{H}(OH)$], 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.7—7.0 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph). Recrystallization of the solid from hexane–AcOEt (10 : 1, v/v) yielded an analytical sample, whose diastereomeric purity was undetermined, as colorless plates, mp 92—93 °C; $[\alpha]_D^{22}$ +16.0° (*c*=1.50, EtOH); IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 1724 (ester CO). *Anal.* Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19; N, 3.07. Found: C, 70.92; H, 8.16; N, 3.34.

(4*S*,5*R*)-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (8)——A stirred mixture of **10** (1.02 g, 2.24 mmol), 1% aqueous AcOH (16 ml), disodium ethylenediaminetetraacetate dihydrate (2.09 g, 5.6 mmol), and $Hg(OAc)_2$ (1.79 g, 5.6 mmol) was heated under reflux for 90 min. After cooling, the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed sequentially with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a reddish oil. The residue was dissolved in a little $CHCl_3$, and the solution was passed through a column packed with alumina (10 g). The column was eluted with $CHCl_3$ and the eluate was evaporated *in vacuo* to leave a reddish-brown oil (965 mg), shown to be a mixture of at least three components on TLC analysis [silica gel, hexane–AcOEt (1 : 3, v/v)]. The oil was then chromatographed on silica gel using hexane–AcOEt (1 : 3, v/v) as eluent. Earlier fractions gave an orange oil (94 mg, 8.2%) presumed[25] to be a mixture of the diastereomeric acetates of **9**, $[\alpha]_D^{25}$ +12.4° (*c*=1.71, EtOH); MS *m/e*: 511 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1632 (lactam CO); NMR ($CDCl_3$) δ: 0.83, 0.91, and 0.99 (3H, t each, *J*=7.5 Hz, diastereomeric *cis*- and *trans*-$CCH_2\underline{Me}$'s), 1.26 (3H, t, *J*=7.2 Hz, $OCH_2\underline{Me}$), 2.06 (3H, s, OCOMe), 3.90 (3H, s, OMe), 4.14 (2H, q, *J*=7.2 Hz, $OC\underline{H}_2Me$), 5.13 (2H, s, $OC\underline{H}_2Ph$), 5.9—6.1 [1H, m, $ArC\underline{H}(OAc)$], 6.75—6.95 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph). The middle fractions afforded an orange oil (231 mg), which produced, after repeated chromatography under different conditions [alumina, hexane–$CHCl_3$ (1 : 3, v/v)], a yellow oil (41 mg, 3.6%) presumed[25] to be a diastereomeric mixture of the acetate of **8**, $[\alpha]_D^{25}$ +2.1° (*c*=1.58, EtOH); MS *m/e*: 511 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1635 (lactam CO); NMR ($CDCl_3$) δ: 0.90 (3H, t, *J*=7.0 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, *J*=7.2 Hz, $OCH_2\underline{Me}$), 2.07 (3H, s, OCOMe), 3.90 (3H, s, OMe), 4.13 (2H, q, *J*=7.2 Hz, $OC\underline{H}_2Me$), 5.14 (2H, s, $OC\underline{H}_2Ph$), 5.9—6.1 [1H, m, $ArC\underline{H}(OAc)$], 6.75—6.95 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph), and yet another yellow oil (157 mg, 15%) presumed[1,13,14] to be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones **9**, $[\alpha]_D^{18}$ +10.3° (*c*=2.00, EtOH); MS *m/e*: 469 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1726 (ester CO), 1610 (lactam CO); NMR ($CDCl_3$) δ: 0.92 and 1.01 (3H, t each, *J*=7.2 and 7.4 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.26 (3H, t, *J*=7.1 Hz, $OCH_2\underline{Me}$), 3.89 (3H, s, OMe), 4.13 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2Me$), 4.8—5.0 [1H, m, $ArC\underline{H}(OH)$], 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.7—7.0 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph).

Later fractions eluted in the first chromatography [silica gel, hexane–AcOEt (1 : 3, v/v)] furnished the 6-piperidone **8** (559 mg, 53%) as a faintly orange oil, $[\alpha]_D^{25}$ −9.6° (*c*=2.00, EtOH); MS *m/e*: 469 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1726 (ester CO), 1618 (lactam CO); NMR ($CDCl_3$) δ: 0.83 and 0.86 (3H, t each, *J*=6.5 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.26 (3H, t, *J*=7.1 Hz, $OCH_2\underline{Me}$), 3.90 (3H, s, OMe), 4.14 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2Me$), 4.50 and 4.66 (1H, d each, *J*=4.4 Hz, diastereomeric OH's), 4.8—5.0 [1H, m, $ArC\underline{H}(OH)$], 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.7—7.05 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph).

(4*S*,5*R*)-(−)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-11]——A solution of **8** (15.4 g, 32.8 mmol) in EtOH (200 ml) containing 70% perchloric acid (3.3 ml) was hydrogenated over 10% Pd–C (5.0 g) at atmospheric pressure and 35 °C for 16 h. The reaction mixture was worked up as described recently[1] for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, giving (−)-**11** (11.8 g, 99%) as an orange oil, $[\alpha]_D^{25}$ −5.7° (*c*=2.00, EtOH); MS *m/e*: 363 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1726 (ester CO), 1625 (lactam CO); NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.1 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, *J*=7.2 Hz, $OCH_2\underline{Me}$), 3.87 (3H, s, OMe), 4.13 (2H, q, *J*=7.2 Hz, $OC\underline{H}_2Me$), 5.75 (1H, s, OH), 6.68 (1H, dd, *J*=7.8 and 1.7 Hz, $H_{(6')}$), 6.75 (1H, d, *J*=1.7 Hz, $H_{(2')}$), 6.85 (1H, d, *J*=7.8 Hz, $H_{(5')}$).

(4*S*,5*R*)-(−)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid [(−)-12]——A solution of (−)-**11** (11.7 g, 32.2 mmol) and 2 N aqueous NaOH (55 ml) in EtOH (110 ml) was stirred at 25 °C for 24 h. The reaction mixture was then worked up as reported recently[1] for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, and (−)-**12** (10.6 g, 98%) was obtained as an orange, glassy gum, $[\alpha]_D^{24}$ −0.2° (*c*=2.00, EtOH); MS *m/e*: 335 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1711 (CO_2H), 1598 (lactam CO); NMR ($CDCl_3$) δ: 0.87 (3H, t, *J*=7.0 Hz, $CCH_2\underline{Me}$), 3.86 (3H, s, OMe), 6.67 (1H, dd, *J*=7.8 and 2.0 Hz, $H_{(6')}$), 6.74 (1H, d, *J*=2.0 Hz, $H_{(2')}$), 6.84 (1H, d, *J*=7.8 Hz, $H_{(5')}$), 7.8 (2H, br, OH and CO_2H).

(4*R*,5*R*)-(+)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid [(+)-13]——The *cis*-lactam acid (−)-**12** (10.0 g, 29.8 mmol) was placed in a small flask and heated neat in an oil bath kept at 180 °C for 90 min. After cooling, the oily reaction mixture was dissolved in AcOEt (25 ml), and the solution was kept in a

refrigerator. The pale brownish pillars that resulted were collected by filtration to give (+)-**13** (3.96 g). The filtrate was concentrated to dryness *in vacuo*, and the residue was again heated at 180 °C for 90 min and worked up as described above. This procedure was repeated 3 more times to raise the yield of (+)-**13** to 74%. Recrystallization of the above pillars from AcOEt yielded an analytical sample as faintly brownish pillars, mp 122.5—123 °C; $[\alpha]_D^{16}$ +68.0° (c=0.500, EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1714 (CO_2H), 1601 (lactam CO); NMR ($CDCl_3$) δ: 0.81 (3H, t, J=7.0 Hz, $CH_2\underline{Me}$), 3.87 (3H, s, OMe), 6.67 (1H, dd, J=8.1 and 2.0 Hz, $H_{(6')}$), 6.73 (1H, d, J=2.0 Hz, $H_{(2')}$), 6.84 (1H, d, J=8.1 Hz, $H_{(5')}$). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.46; H, 7.57; N, 4.16.

(4*R*,5*R*)-(+)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-14]——A solution of (+)-**13** (6.20 g, 18.5 mmol) in 10% (w/w) ethanolic HCl (120 ml) was stirred at 15 °C for 24 h. The reaction mixture was worked up as described recently[1] for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, producing (+)-**14** (6.65 g, 99%) as an orange oil, $[\alpha]_D^{16}$ +66.8° (c=0.500, EtOH); MS m/e: 363 (M^+). The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra and TLC behavior of this sample were identical with those of authentic (±)-**14**.[10]

(4*R*,5*R*)-(+)-1-(4-Benzyloxy-3-methoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-17]——A stirred mixture of (+)-**14** (6.40 g, 17.6 mmol), anhydrous K_2CO_3 (2.92 g, 21.1 mmol), benzyl bromide (3.60 g, 21.0 mmol), and acetone (80 ml) was heated under reflux for 26 h. The reaction mixture was then worked up as described recently[10] for the corresponding racemic variety, and (+)-**17** (7.64 g, 96%) was obtained as a yellow oil, $[\alpha]_D^{15}$ +55.0° (c=0.500, EtOH); MS m/e: 453 (M^+). The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra and TLC behavior of this oil were identical with those of authentic (±)-**17**.[10]

(2*R*,3*R*)-10-Benzyloxy-2-ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9-methoxybenzo[*a*]quinolizinium Chloride (16)——A solution of (+)-**17** (2.04 g, 4.5 mmol) and $POCl_3$ (3.45 g, 22.5 mmol) in dry toluene (21 ml) was heated under reflux for 90 min. The reaction mixture was worked up as described recently[10] for the racemic series, giving **16** (2.48 g) as a brown oil. This oil was directly used in the next hydrogenation step without further purification.

(2*R*,3*R*,11b*S*)-(−)-10-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(−)-15]——A solution of the total amount of crude **16** described above in EtOH (35 ml) was hydrogenated over Adams catalyst (180 mg) at atmospheric pressure and room temperature for 60 min. The reaction mixture was then worked up in a manner similar to that described recently[1] for the 9-benzyloxy-10-methoxy isomer, and the resulting brown solid (1.63 g) was recrystallized from ether to give (−)-**15** (1.38 g, 70%). Further recrystallization from ether furnished an analytical sample as faintly yellow needles, mp 99—99.5 °C; $[\alpha]_D^{16}$ −46.0° (c=0.500, EtOH). *Anal.* Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.02; H, 8.08; N, 3.22. The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra and TLC behavior of this sample were identical with those of authentic (±)-**15**.[10]

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References and Notes

1) Paper XI in this series, T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 583 (1985).
2) K. R. Kirtikar and B. D. Basu, "Indian Medicinal Plants," 2nd ed., Vol. II, L. M. Basu, Allahabad, India, 1933, pp. 1236—1239.
3) R. N. Chopra, I. C. Chopra, K. L. Handa, and L. D. Kapur, "Indigenous Drugs of India," 2nd ed., U. N. Dhar and Sons, Calcutta, 1958, pp. 270—271.
4) B. Dasgupta, *J. Pharm. Sci.*, **54**, 481 (1965).
5) For recent reviews, see *a*) T. Fujii and M. Ohba, "The Alkaloids," Vol. XXII, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1; *b*) T. Fujii, *Yakugaku Zasshi*, **103**, 257 (1983).
6) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **27**, 1486 (1979).
7) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron*, **36**, 965 (1980).
8) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477.
9) T. Fujii, K. Yamada, S. Minami, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **31**, 2583 (1983).
10) T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 144 (1985).
11) T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, *Heterocycles*, **14**, 971 (1980).
12) T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, *Heterocycles*, **19**, 2305 (1982).
13) T. Fujii and S. Yoshifuji, *Tetrahedron*, **36**, 1539 (1980).
14) T. Fujii and S. Yoshifuji, *J. Org. Chem.*, **45**, 1889 (1980).
15) T. Fujii, H. Kogen, and M. Ohba, *Tetrahedron Lett.*, **1978**, 3111.
16) T. Fujii and M. Ohba, *Heterocycles*, **19**, 857 (1982).
17) T. Fujii, M. Ohba, and H. Suzuki, *Heterocycles*, **19**, 705 (1982).
18) For the stereochemistry of this ester, see *a*) V. Prelog and E. Zalán, *Helv. Chim. Acta*, **27**, 535 (1944); *b*) *Idem, ibid.*, **27**, 545 (1944).

19) For a review on this *Cinchona* alkaloid, see W. Solomon, "Chemistry of the Alkaloids," ed. by S. W. Pelletier, Van Nostrand Reinhold, New York, 1970, Chapter 11.
20) A. Kaufmann, E. Rothlin, and P. Brunschweiler, *Ber. Dtsch. Chem. Ges.*, **49**, 2299 (1916).
21) *a*) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.*, **21**, 2695 (1973); *b*) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 2336 (1977); *c*) T. Fujii, T. Hiraga, and M. Ohba, *ibid.*, **29**, 2691 (1981).
22) T. Fujii, M. Ohba, S. Yoshifuji, and S. Akiyama, Abstracts of Papers, 9th International Congress of Heterocyclic Chemistry, Tokyo, August 1983, p. 237.
23) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **26**, 2253 (1978).
24) B. Leopold, *Acta Chem. Scand.*, **4**, 1523 (1950) [*Chem. Abstr.*, **45**, 7049*g* (1951)].
25) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **20**, 1451 (1972).